Synergistic Effect of Co-Spray Dried Colistin and Azithromycin for the Treatment of Lower Respiratory Infections

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Synergistic Effect of Co-Spray Dried Colistin & Azithromycin for Treatment of Lower Respiratory Infections

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LSAMP PURDUE

Background

An ongoing focus of pharmaceutical research is enhancing the efficacy of inhaled drugs indicated to treat lower respiratory infections. To achieve this, an inhaled drug must exhibit a high aerosolisation performance, or the ability of fine particles to disperse and reach the target site in the lower respiratory passageways. Proper deposition of the aerosol particles at the site of action is dependent upon chemical properties and the aerodynamic diameter. Preliminary data demonstrated that the aerosolisation performance of colistin, a hydroscopic antibiotic, notably decreased when stored at a relative humidity (RH) of 75% due to moisture absorption. To prevent moisture absorption, my aim is to combine two antibiotics, colistin and azithromycin, into one formulation to improve the combination drug's delivery to the target site of action and produce a synergistic effect. The use of azithromycin, an antibiotic that exhibits hydrophobic properties, would minimize water absorption and increase the drug's efficacy. A better understanding of colistin and azithromycin's aerosolisation properties is important in strengthening therapeutic methods to treat individuals with specific pulmonary disorders.

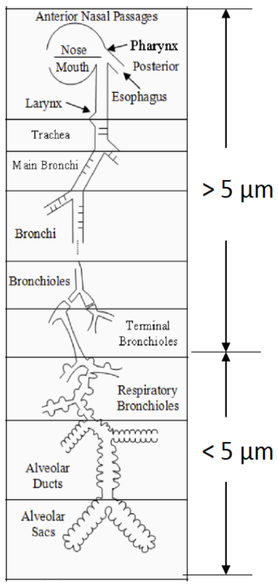


Figure 1 (left): Particles with aerodynamic sizes 1-5 um will mostly deposit in the lower airways, while particles with aerodynamic sizes > 5 um will normally deposit in the upper airways due to inertial impaction.[1]

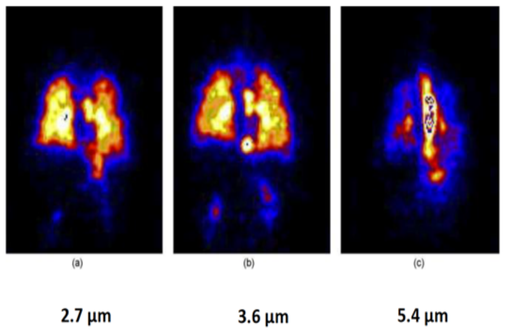


Figure 2 (above): Distribution of radiolabeled powder aerosols of mannitol in the lungs using single photon emission tomography (SPECT).[1]

An important factor influencing lung deposition and the efficacy of inhaled drugs is particle size, or aerodynamic diameter (um). In regards to particle size, the FPF value, or fine particle fraction, is the value of interest, and it is the fraction of the total drug dose < 5.0 um.[2] Our research goal is to obtain an FPF value of > 50%.

Hypothesis

We hypothesize that encapsulating colistin with azithromycin will improve drug stability by preventing moisture absorption, and therefore, enhance dispersion to the target site and overall aerosolisation performance.

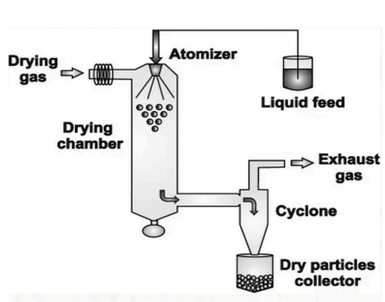
Research Goal

1) Optimize spray-drying process for 3-fluid nozzle by manipulating three independent variables: flow rate, inlet temperature, and feed concentration
2) Understand the mixing behavior with 3-fluid nozzle

Methods

1) Spray Drying (Colistin:Azithromycin, 1:1)

Spray drying is a dehydration process in which a liquid is converted to a powder form. Compressed air atomizes the solution into fine droplets, followed by a rapid drying process by hot gas, resulting in a fine powder.[6]



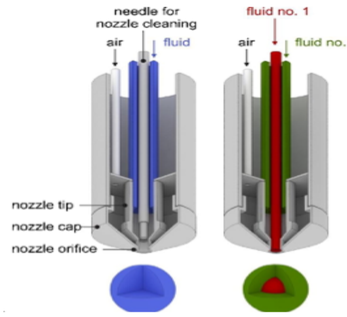
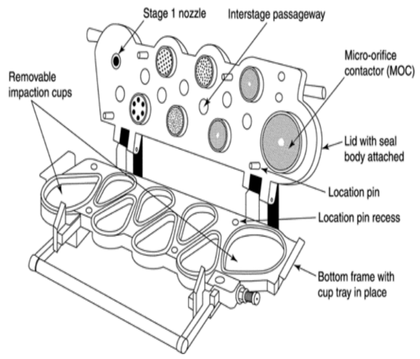


Figure 3: A 3-fluid nozzle spray drying system consists of three separate channels, one each for the 1) core, 2) shell liquid, and 3) atomising gas. The shell and core liquids arrive at the tip of the nozzle to form a concentric liquid, which is atomized and dried by hot gas to produce the core-shell microcapsules.[6]

2) Next Generation Impactor (NGI)



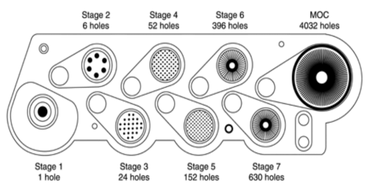


Figure 4: Larger particles with a greater aerodynamic diameter will deposit in the earlier stages while the smallest particles will deposit in the latter stages, specially in MOC, a collection cup that captures extremely small particles.[3]

The NGI measures in-vitro aerosol performance and is used to classify aerosol particles into size fractions for testing dry powder inhalers. Essentially, this device mimics the human respiratory system and consists of 8 stages, with the early stages representing the upper airways (stage 1: human throat) and the latter stages mimicking the lower airways (stage 8: alveoli of lungs). Air passes through the impactor, and particle sizing is achieved by forcing the air stream through a series of nozzles containing progressively reducing jet diameters. The fine particles from each stage are collected in a series of collection cups.[5]

3) High-performance liquid chromatography (HPLC)

HPLC is performed to separate, identify, and quantify the mixture of azithromycin and colistin. A pump forces the mixture through a column under high pressure. Azithromycin and colistin are separated from one another due to different interactions with the stationary phase or column material. Each component possesses a distinct retention time, or the time it takes for a solute to pass through the column. The computer output displays a series of peaks, each one representing a component in the mixture passing through the detector and absorbing UV light.[4]

Results

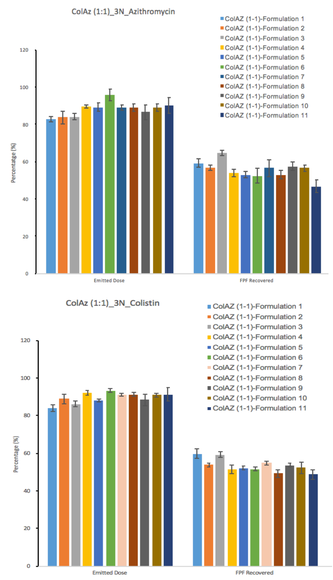


Figure 6 (left): The two graphs display the values for emitted dose (% of drug emitted from capsule and device that is deposited in the throat and 8 stages) and the values for FPF, which surpassed the target goal of 50%. The optimal formulation was selected based on the FPF value and percent yield.

Formulation	Flow Rate	Inlet Temp	Feed Concentration	%yield	ED-colistin (%)	FPF-colistin (%)	ED-azithromycin (%)	FPF-azithromycin (%)
1	4 mL/min	120°C	10 mg/mL	54.59%	87.0±1.8	59.8±2.5	82.6±1.5	59.2±2.5
2	4 mL/min	150°C	30 mg/mL	52.55%	89.0±2.6	53.8±1	83.7±3.4	56.6±1.4
3	4 mL/min	150°C	10 mg/mL	70.12%	86.3±1.7	59.3±1.7	84.1±1.5	64.7±1.3
4	8 mL/min	120°C	10 mg/mL	79%	92.3±1.3	51.5±2.5	89.7±0.9	53.8±1.8
5	8 mL/min	150°C	10 mg/mL	70.99%	88.2±0.9	52.1±1	89.2±2.1	53.0±1.5
6	4 mL/min	120°C	30 mg/mL	82.92%	93.4±1.2	51.7±1.2	95.6±3	52.3±4
7	8 mL/min	120°C	30 mg/mL	69.81%	91.1±0.7	54.8±0.9	89.1±1.5	56.4±4.7
8	6 mL/min	135 °C	20 mg/mL	84.15%	91.3±0.9	49.4±2	89±2	52.9±2.3
9	6 mL/min	135 °C	20 mg/mL	80%	88.5±3.1	53.6±1	86.5±4	57.5±2.5
10	6 mL/min	135 °C	20 mg/mL	77.66%	90.9±0.8	52.3±2.9	88.8±2	56.4±1.8
11	8 mL/min	150°C	30 mg/mL	80%	91.2±0.5	48.8±2.5	90.2±4.2	46.5±3.4

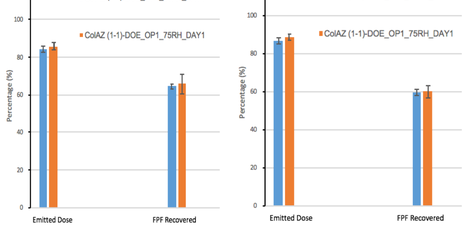
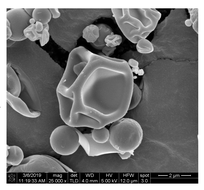


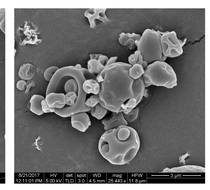
Figure 7 (above) : Eleven different formulations were performed with varying flow rates, inlet temperatures, and feed concentrations.

Figure 8 (left): The graphs show there was no significant difference in the FPF values when optimal formulation #3 was exposed to 20% RH for 24 hours and 75% RH for 24 hours.

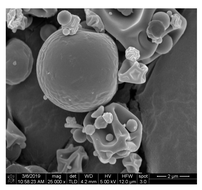
Figure 9 (right): Results produced from SEM (scanning electron microscopy) depict small particles adhesive to larger particles. The small particles represent azithromycin surrounding the colistin core, the larger particle.



20%RH – Day 1



75% RH – Day 10



75% RH – 1 month

Discussion

The graphs suggest azithromycin in combination with colistin successfully prevented moisture absorption due to no significant changes in FPF values as RH increased. In other words, the combination of azithromycin and colistin improved drug stability at greater humidity levels and overall aerosolisation performance. Furthermore, the data suggest that rather than coating colistin, azithromycin acts to minimize the interfacial tension between colistin and water particles, ultimately preventing aggregation.

Acknowledgements

Thank you to the sponsors of LSAMP. Special thanks to Nivedita Shetty, Patricia Ahn, and Dr. Zhou for their patience, guidance, and mentoring.

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